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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/466,935	12/20/1999	VITALIY ARKADYEVICH LIVSHITS	US-126O	1750

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EXAMINER	
STEADMAN, DAVID J	

ART UNIT	PAPER NUMBER
1656	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/466,935	LIVSHITS ET AL.	
	Examiner	Art Unit	
	David J. Steadman	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 November 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *77-84* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *77-84* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10/15/08, 11/6/08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☒ Other: *Appendix A sequence alignment*.

DETAILED ACTION

Status of the Application

[1] In view of the new ground of rejection is set forth below after the appeal brief filed on 11/17/08 (hereafter referred to as the "Brief"), PROSECUTION IS HEREBY REOPENED.

To avoid abandonment of the application, appellant must exercise one of the following two options:

(1) file a reply under 37 CFR 1.111 (if this Office action is non-final) or a reply under 37 CFR 1.113 (if this Office action is final); or,

(2) initiate a new appeal by filing a notice of appeal under 37 CFR 41.31 followed by an appeal brief under 37 CFR 41.37. The previously paid notice of appeal fee and appeal brief fee can be applied to the new appeal. If, however, the appeal fees set forth in 37 CFR 41.20 have been increased since they were previously paid, then appellant must pay the difference between the increased fees and the amount previously paid.

A Supervisory Patent Examiner (SPE) has approved of reopening prosecution by signing below.

[2] Claims 77-84 are pending in the application.

[3] Receipt of information disclosure statements filed on 10/15/08 and 11/6/08 is acknowledged.

[4] Applicant's arguments presented in the Brief filed on 11/17/08 in response to the final Office action mailed on 7/22/08 have been fully considered and are deemed to be persuasive to overcome at least one of the rejections and/or objections previously

applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

[5] The text of those sections of Title 35 U.S. Code not included in the instant action can be found in a prior Office action.

Information Disclosure Statement

[6] With the exception of the document identified as "Copy of NOTICE OF OPPOSITION for European Patent App. No. 99125406.1", all documents cited in the IDS filed on 11/6/08 have been considered by the examiner.

The document identified as "Copy of NOTICE OF OPPOSITION for European Patent App. No. 99125406.1" has not been considered as the document is not in the English language and fails to satisfy the requirements of 37 CFR 1.98.(a)(3)(i), which requires "A concise explanation of the relevance, as it is presently understood by the individual designated in § 1.56(c) most knowledgeable about the content of the information, of each…publication…that is not in the English language".

[7] The IDS filed on 11/6/08 identifies the IDS filed on 10/15/08 as having a typographical error and is intended to replace the IDS filed on 10/15/08. Moreover, the documents cited in the IDS filed on 10/15/08 are duplicates of those cited in the 11/6/08 IDS. As such, the citations on the 10/15/08 IDS have been lined through.

Claim Rejections - 35 USC § 112, First Paragraph

[8] Claims 77-80 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for the increased production of L-homoserine and L-threonine in a culture medium, does not reasonably provide enablement for a method for the increased production of any L-amino acid in the culture medium.

"The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue." *In re Angstadt*, 537 F.2d 498, 504, 190 USPQ 214, 219 (CCPA 1976). Factors to be considered in determining whether undue experimentation is required are summarized in *In re Wands* (858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)) as follows: (A) The breadth of the claims; (B) The nature of the invention; (C) The state of the prior art; (D) The level of one of ordinary skill; (E) The level of predictability in the art; (F) The amount of direction provided by the inventor; (G) The existence of working examples; and (H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure. See MPEP § 2164.01(a). The Factors considered to be most relevant to the instant rejection are addressed in detail below.

The breadth of the claims: Claim 77 is drawn to "a method of producing an L-amino acid…wherein said amino acid is present in the medium…in a larger amount". The specification fails to provide a limiting definition of the term "amino acid" and while the specification expressly discloses L-homoserine, L-threonine, L-valine, L-leucine, and L-isoleucine (p. 21, lines 15-20) these are disclosed as being exemplary and non-

limiting. As such, claim 77 (claims 78-80 dependent therefrom) has been interpreted as encompassing a method for producing *any* amino acid. The enablement provided by the specification is not commensurate in scope with the claims with regard to the broad scope of amino acids whose production is increased. In this case, the specification is enabling only for a method for the increased production of L-homoserine and L-threonine in a culture medium.

The amount of direction provided by the inventor and The existence of working examples: The specification discloses that a bacterium overepxressing an *E. coli rhtC* gene (SEQ ID NO:3) produces L-threonine, L-homoserine, L-valine, and L-leucine (*e.g.,* pp. 34, Table 5). However, with respect to those amino acids whose production is increased, the specification discloses that only L-threonine and L-homoserine were present in a larger amount in the culture medium (pp. 30-34), with decreased production of L-valine and L-leucine. While the specification provides guidance for increasing production of L-valine and L-leucine, which requires co-expression of an *E. coli rhtB* gene (p. 34, Table 5), the specification fails to provide any specific guidance regarding alterations to an *Escherichia* bacterium overexpressing SEQ ID NO:3 that result in the increased production of any amino acid.

The state of the prior art; The level of one of ordinary skill; and The level of predictability in the art: While the prior art acknowledges that *E. coli* is used as a production host for threonine, tryptophan, and valine, it is not recognized as being used to produce *any* L-amino acid as encompassed by the claims. See, *e.g.,* Jetten et al. *Crit. Rev. Biotechnol.* 15:73-103, 1995.

The quantity of experimentation needed to make or use the invention based on the content of the disclosure: While the use of *E. coli* for producing certain L-amino acids was known in the art at the time of the invention, it was not routine in the art to use *E. coli* for the production of any amino acid in a culture medium.

In view of the overly broad scope of the claims, the lack of guidance and working examples provided in the specification, the high level of unpredictability as evidenced by the prior art, and the amount of required experimentation, it is the examiner's position that undue experimentation would be necessary for a skilled artisan to make and use the entire scope of the claimed invention. Applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims. The scope of the claims must bear a reasonable correlation with the scope of enablement (*In re Fisher*, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Claim Rejections - 35 USC § 103

[9] Upon further consideration, the rejection of claims 77-84 under 35 U.S.C. 103(a) as set forth at paragraph [10] at pp. 3-11 of the Office action mailed on 7/22/08 is withdrawn. In view of the disclosure of the specification, one of ordinary skill in the art would not reasonably interpret the method of Kobayashi alone or in combination with

the references of Kaplan, Georgiou, and Begot as encompassing a step of "removing solids including cells from the medium" and "purifying said L-amino acid from the medium obtained in step B)".

[10] Claims 77-84 are rejected under 35 U.S.C. 103(a) as being unpatentable over Debabov et al. (US Patent 4,321,325; hereafter referred to as "Debabov") in view of Vrlijc et al. (US Patent 6,858,406; cited in the IDS filed on 11/6/08; hereafter referred to as "Vrlijc"), Daniels et al. (NCBI Database Accession Number P27846, July 1998; cited in the IDS filed on 11/6/08; hereafter referred to as "Database Accession Number P27846"), Daniels et al. (*Science* 257:771-778, 1992; cited in the IDS filed on 1/26/07; hereafter referred to as "Daniels"), and Kobayashi et al. (*J. Biochem.* 98:1007-1016, 1985; cited in the IDS filed on 1/26/07; hereafter referred to as "Kobayashi") and as evidenced by Zakataeva et al. (*FEBS Lett.* 452:228-232, June 1999; cited in the IDS filed on 5/31/00; hereafter referred to as "Zakataeva").

Claim 77 is drawn to a method for producing an amino acid by: A) culturing in a culture medium a bacterium that is transformed with a DNA encoding SEQ ID NO:4; B) removing solids including cells from the medium; and C) purifying said amino acid from the medium obtained in step B), wherein the L-amino acid is present in a larger amount. Claim 78 limits the sequence of the DNA encoding SEQ ID NO:4 to comprising nucleotides 187 to 804 of SEQ ID NO:3. Claim 79 further limits the bacterium to being transformed with a second DNA that encodes SEQ ID NO:2. Claim 80 further limits the sequence of the DNA encoding SEQ ID NO:2 to comprising nucleotides 557 to 1171 of

SEQ ID NO:1. Claims 81-84 limit the L-amino acid produced by the method of claims 77-80 to being L-threonine.

The reference of Debabov teaches *Escherichia coli* is used for production of L-threonine (column 1, line 38 to column 2, line 23) and acknowledges a desire for increased accumulation of L-threonine in a culture medium over known methods (column 2, lines 36-39). Debabov teaches an *E. coli* transformed with an expression vector comprising an *E. coli* chromosomal fragment containing all of the genes of the threonine operon (column 3, lines 14-44) and a method for producing L-threonine using this *E. coli,* which involves culturing the *E. coli,* separating the cells from the liquid medium, and purifying the L-threonine (column 5, lines 20-64). According to Debabov, their *E. coli* results in an enhanced production of L-threonine (column 6, lines 21-31). The difference between the teachings of Debabov and the claimed method is that the *E. coli* of Debabov is not transformed with a DNA encoding SEQ ID NO:4.

The reference of Vrlijc teaches the use of *Escherichia coli* in the production of L-amino acids (column 1, lines 24-32) and teaches that numerous methods of modifying the bacteria to improve production have been carried out (column 1, line 33 to column 2, line 4). According to Vrlijc, these attempts to increase L-amino acid production are directed to cytosolic synthesis and suggests that export of the L-amino acids should be considered – specifically noting improved export – as a method for increasing efficiency of L-amino acid production (column 2, lines 8-15). Vrlijc acknowledges that methods for enhancing L-amino acid export have been non-directed and non-specific with respect to the exported L-amino acid or the target of modification (column 2, lines 17-24). As a

remedy to previous methods, Vrlijc suggests enhancing production of an L-amino acid exporter, teaching that "The increased export expression or respectively, activity of the export carrier resulting from this process leads to an increased secretion rate so that the export of the respective amino acid is increased. The microorganisms so modified also accumulate an increased part of the respective amino acid in the culture medium". Although Vrlijc teaches enhancing expression of an L-amino acid export polypeptide is a method for improving L-amino acid production, Vrlijc fails to expressly teach enhancing expression of the polypeptide of SEQ ID NO:4.

The reference of Database Accession Number P27846 teaches the sequence of an *E. coli* polypeptide that is identified as being encoded by the *E. coli recQ-pldB* intergenic region and is annotated as being a threonine efflux polypeptide. The polypeptide of Database Accession Number P27846 is 100% identical to SEQ ID NO:4 herein (see **Appendix A** sequence alignment).

The reference of Daniels shows that the *E. coli recQ-pldB* intergenic region is flanked on the 5'-end by *pldA* and on the 3'-end by *pldB* (p. 773, top). In other words, the *E. coli recQ-pldB* intergenic region is entirely between *pldA* and *pldB.*

The reference of Kobayashi discloses expression vectors, *e.g.,* pAB104 and pA1042, comprising the region of the *E. coli* chromosome between *pldA* and *pldB* (p. 1012, Figure 4). Applicant acknowledges the vector of Kobayashi comprises the DNA of SEQ ID NO:3, which encodes the polypeptide of SEQ ID NO:4 (*e.g.,* Brief at p. 6, middle). Evidentiary reference Zakataeva is cited in accordance with MPEP 2131.01.III as showing that a characteristic not disclosed in the reference of Kobayashi is inherent.

Namely, Zakataeva teaches the *E. coli rhtC* gene (SEQ ID NO:3) and the *E. coli rhtB* gene (SEQ ID NO:1) are present between the *E. coli pldA* and *pldB* genes in the *E. coli* genome (p. 229, Figure 1). As such, the vectors of Kobayashi necessarily comprise both the *E. coli rhtC* and *rhtB* genes.

At the time of the invention, it would have been obvious to one of ordinary skill in the art to transform the *E. coli* of Debabov with the vector of Kobayashi and practice the L-threonine production method as taught by Debabov. One would have been motivated to do this because: 1) the method of Debabov is directed to L-threonine production; 2) in view of the references of Database Accession Number P27846, Daniels, and Kobayashi, one would have recognized the vector of Kobayashi comprises a nucleic acid encoding a polypeptide, which, according to Database Accession Number P27846 is asserted to be a threonine efflux polypeptide; and 3) Vrlijc expressly teaches increased production of an L-amino acid by enhancing expression of its respective export polypeptide. One would have had a reasonable expectation of success to transform the *E. coli* of Debabov with the vector of Kobayashi and practice the L-threonine production method as taught by Debabov because of the results of Debabov, Vrlijc, and Kobayashi. Therefore, the method of claims 77-84 would have been obvious to one of ordinary skill in the art at the time of the invention.

RESPONSE TO ARGUMENT: To the extent the rejection under 35 U.S.C. 103(a) is based on the reference of Kobabyashi, applicant's arguments are addressed below.

Beginning at p. 5 of the Brief, applicant argues Kobayashi is not concerned with L-amino acid production and the secondary references fail to remedy this defect.

It is the examiner's position that in view of the new combination of references – particularly the newly cited references of Vrlijc, Daniels, and Database Accession Number P27846 in the IDS filed on 11/6/08 – one of ordinary skill in the art would have recognized that the threonine efflux polypeptide of Database Accession Number P27846 was encoded by the vector of Kobayashi and would have been motivated to use the vector of Kobayashi in the host cell and method of Debabov. As such, the method of claims 77-84 would have been obvious to one of ordinary skill in the art at the time of the invention.

Conclusion

[11] Status of the claims:

Claims 77-84 are pending.

Claims 77-84 are rejected.

No claim is in condition for allowance.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David J. Steadman whose telephone number is 571-272-0942. The examiner can normally be reached on Mon to Fri, 7:30 am to 4:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jon P. Weber can be reached on 571-272-0925. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/David J. Steadman/
Primary Examiner, Art Unit 1656

/JON P WEBER/
Supervisory Patent Examiner, Art Unit 1656/7

APPENDIX A

Query sequence 1

>YIGJ (Database Accession Number P27846)
MLMLFLTVAMVHIVALMSPGPDFFFVSQTAVSRSRKEAMMGVLGITCGVMVWAGIALLGL
HLIIEKMAWLHTLIMVGGGLYLCWMGYQMLRGALKKEAVSAPAPQVELAKSGRSFLKGLL
TNLANPKAIIYFGSVFSLFVGDNVGTTARWGIFALIIVETLAWFTVVASLFALPQMRRGY
QRLAKWIDGFAGALFAGFGIHLIISR

Query sequence 2

>SEQ ID NO:4
MLMLFLTVAMVHIVALMSPGPDFFFVSQTAVSRSRKEAMMGVLGITCGVMVWAGIALLGL
HLIIEKMAWLHTLIMVGGGLYLCWMGYQMLRGALKKEAVSAPAPQVELAKSGRSFLKGLL
TNLANPKAIIYFGSVFSLFVGDNVGTTARWGIFALIIVETLAWFTVVASLFALPQMRRGY
QRLAKWIDGFAGALFAGFGIHLIISR

Full-length alignment between two sequences

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>>SEQ ID NO:4                                              (206 aa)
 s-w opt: 1356  Z-score: 1669.9  bits: 315.9 E(): 3.3e-91
Smith-Waterman score: 1356;  100.000% identity (100.000% ungapped) in 206 aa overlap (1-206:1-
206)

               10        20        30        40        50        60
YIGJ   MLMLFLTVAMVHIVALMSPGPDFFFVSQTAVSRSRKEAMMGVLGITCGVMVWAGIALLGL
       ::::::::::::::::::::::::::::::::::::::::::::::::::::::::::::::
SEQ    MLMLFLTVAMVHIVALMSPGPDFFFVSQTAVSRSRKEAMMGVLGITCGVMVWAGIALLGL
               10        20        30        40        50        60

               70        80        90       100       110       120
YIGJ   HLIIEKMAWLHTLIMVGGGLYLCWMGYQMLRGALKKEAVSAPAPQVELAKSGRSFLKGLL
       ::::::::::::::::::::::::::::::::::::::::::::::::::::::::::::::
SEQ    HLIIEKMAWLHTLIMVGGGLYLCWMGYQMLRGALKKEAVSAPAPQVELAKSGRSFLKGLL
               70        80        90       100       110       120

              130       140       150       160       170       180
YIGJ   TNLANPKAIIYFGSVFSLFVGDNVGTTARWGIFALIIVETLAWFTVVASLFALPQMRRGY
       ::::::::::::::::::::::::::::::::::::::::::::::::::::::::::::::
SEQ    TNLANPKAIIYFGSVFSLFVGDNVGTTARWGIFALIIVETLAWFTVVASLFALPQMRRGY
              130       140       150       160       170       180

              190       200
YIGJ   QRLAKWIDGFAGALFAGFGIHLIISR
       :::::::::::::::::::::::::::
SEQ    QRLAKWIDGFAGALFAGFGIHLIISR
                190       200
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